C1 34. (Amended) A method for treating a patient with a painful condition of the anal region associated with muscle spasm, the method comprising:

providing a topical pharmaceutical composition comprising an α-adrenergic blocker; and topically applying an effective dose of the composition to the anal region.

C2 37. (Amended) The method of claim 34, wherein said blocker is doxazosin.

C3 42. (Amended) The method of claim 34 wherein said composition is dry, a liquid, a cream, or an aerosol.

REMARKS

A. Status of the Claims

Claims 34-40 and 42-48 are pending and presented for examination. Claims 34, 37 and 42 are herein amended. Claim 41 has been canceled without prejudice.

Claim 37 stands objected to for a typographical error.

Claims 34-48 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Kubota et al. (*J. Smooth Muscle Res.* 34:173 (August 1998)) or Bouvier et al. (*J. Physiol.* 310:457 (1981)) in view of Fogel (U.S. Patent No. 6,159,944), Pasricha et al. (U.S. Patent No. 5,437,291) or Singh et al. (U.S. Patent No. 5,858,371).

With respect to the Request for an Interference, the Request was not accepted at the present time but states that the request for interference will be considered for a future possible interference.

Applicants respectfully repeat their request for an interference and provide a traversal of the 35 U.S.C. §103(a) rejection.

B. Amendments to the Claims

The Amendments to the claims add no new subject matter.

The recitals of the "topical pharmaceutical composition" and "topically applying" in the base claim find support in claim 35 and canceled claim 41 which respectively recited "pharmaceutically acceptable carrier" and "topical formulation" as well as throughout the specification and many Examples which illustrated topical application to the anorectal area.

Claim 37 was amended to correct a typographical error with respect to the term "doxazosin."

Claim 42 was amended to correct an antecedent basis due to the cancellation of intervening claim 41.

As such, Applicants respectfully request that the amendments be entered.

C. Request for Interference

The present application, i.e., U.S. Patent Application Serial No. 09/769,621, filed January 23, 2001, is a Continuation of U.S. Patent Application No. 09/460,306 filed December 13, 1999, which claims priority from U.S. Provisional Applications 60/112,325, filed December 14, 1998; 60/139,916, filed June 17, 1999, 60/155,318, filed September 21, 1999, and 60/222,267, filed July 31, 2000. The present application also claims the benefit of U.S. Patent Application Serial No 09/595,390, filed June 14, 2000, the disclosures of which are incorporated in this application by reference in their entirety.

Applicants respectfully request that an interference be declared under 37 C.F.R. §1.607 between the present application and U.S. Patent No. 6,117,877 issued to Fogel on September 12, 2000. In view of the priority listed above, and the lack of the disclosure of the claimed subject matter in the priority document of U.S. Patent No. 6,117,877 (see the Preliminary Amendment and Request for Interference filed on July 27, 2001), Applicants believe that Applicants would be senior party in any interference proceedings. Applicants are the first to file and would like an opportunity to show that they were first to invent and therefore entitled to the patent.

D. Response to the Objection of Claim 37

Claim 37 has been amended to correct the typographical error related to the term "doxazosin." Applicants request the objection be reconsidered and withdrawn.

E. Traversal of the Rejections Under 35 U.S.C. §103(a)

The Action rejects claims 34-48 under 35 U.S.C. §103(a) as being allegedly obvious over Kubota et al. (*J. Smooth Muscle Res.* 34:173 (August 1998)) or Bouvier et al. (*J. Physiol.* 310:457 (1981)) in view of Fogel (U.S. Patent No. 6,159,944) ("Fogel 944"), Pasricha et al. (U.S. Patent No. 5,437,291) or Singh et al. (U.S. Patent No. 5,858,371).

Applicants respectfully disagree with the Action and provide traversals of the 35 U.S.C. §103 rejections below.

1. Standard of Review Under 35 U.S.C. 103(a)

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established.

As amended, base claim 34 recites:

> A method for treating a patient with a painful condition of the anal region associated with muscle spasm, the method comprising :
> providing a topical pharmaceutical composition comprising an α-adrenergic blocker; and
> topically applying an effective dose of the composition to the anal region.

2. The proposed combination of Kubota et al. in view of Singh et al. does not teach all the elements of the claims.

The above particular combination of the proposed references does not teach all the elements of the claims. The Action first cites Kubota et al. as teaching a method of relaxing the internal anal sphincter including the use of an α_1-adrenergic antagonist such as "phentolamine, tetrodotoxin and atropine."

However, atropine is **not** an α_1-adrenergic antagonist (see col. 4, lines 38-40 of Singh et al.). The Action cited Singh et al. as allegedly disclosing *atropine* as an effective treatment for any anorectal disorder. However, atropine is a muscarinic cholinergic antagonist and not an α-adrenergic antagonist. As such, the proposed combination of Kubota et al. and Singh et al. does not include an α-adrenergic antagonist as recited in the base claim.

Thus, Applicants request that the rejections based upon the combination of Kubota in view of Singh et al. be reconsidered and withdrawn.

> PRIOR ART MUST BE CONSIDERED IN ITS ENTIRETY, INCLUDING DISCLOSURES THAT TEACH AWAY FROM THE CLAIMS A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984) Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), cert.denied, 464 U.S. 1043 (1984).

Based upon the entirety of their disclosures, Fogel, Pasricha et al. and Singh et al., show that one of ordinary skill in the art would not have expected the proposed combination to work:

i. Both Pasricha et al. and Fogel teach the regulation of the IAS *in vivo* is too complex a subject matter to afford any reasonable expectation of success with respect to the combination proposed by the Action:

As evidenced in Pasricha et al., one of ordinary skill in the art would not have had a reasonable expectation of success that the proposed substitution would work. Pasricha et al. teach the unpredictability of the subject matter at col. 1, line 45 – col. 2 line 30:

> ...Both skeletal and smooth muscle in the gastrointestinal tract are under the control of the enteric nervous system which is an extremely complex network of nerves and muscles, that resides within the gastrointestinal wall and orchestrates the entire digestive process including motility, secretion and absorption. The enteric nerves are also organized into interconnected networks called plexuses. Of these, the myenteric plexus, situated between the circular and longitudinal muscle layers, is the main modulator of gastrointestinal motility. It receives input from both the central nervous system (via vagal and sympathetic pathways) as well as from local reflex pathways. Its output consists of both inhibitory and excitatory signals to the adjacent muscle...
>
> Finally, the myenteric plexus is probably the most important but not the only determinant of muscle tone in the gastrointestinal tract. In fact, basal smooth muscle tone may be visualized as resulting from the sum of many different factors including intrinsic (myogenic) tone, and circulating hormones, in addition to nerve activity.
>
> ... **While there have been isolated reports on the effects of botulinum toxin on in vitro preparations of gastrointestinal smooth muscle, the regulation of gastrointestinal muscle is so complex that the physiological consequences of blocking neurotransmitter release (by using toxin such as botulinum) in humans or in live animals were not predictable prior to the present invention** (emphasis added).

Moreover, in a continuation application (U.S. Patent No. 6,117,877) (Fogel, '877) of the Fogel '944 patent, **Fogel expressly teaches specifically with respect to the very subject matter of the claims that the subject matter is too unpredictable to sustain a reasonable expectation of success:**

> The innervation of the internal anal sphincter (IAS) is complex, involving adrenergic, cholinergic, and non-adrenergic non-cholinergic nerves. In general, α-adrenergic stimulation contracts the sphincter, and β-adrenergic stimulation relaxes it. (Penninckx et al.; Baillieres Clin Gastroenterol, 1992 March 6:193-214; O'Kelly T, et al., Gut, 1993 34:689-93; May and Nissan et al., J Pediatr Surg, 1984 February 19:12-4; Tottrup et al., Br J Pharmacol, 1995 May, 115:158-62,; Sumitomo et al., Z Kinderchir, 1986 February 41:35-8).
>
> Contraction of the IAS in response to hypogastric (sympathetic) nerve stimulation, or spasm of the IAS in response to local stimulation, is attenuated by α1-adrenergic antagonists and by non-specific α-adrenergic antagonists. In its response to α-agonists and antagonists, the IAS responds like the internal urethral sphincter, with which it shares a common developmental origin. As expected, phenylephrine, an alphal agonist, increases tone in the IAS. However, it is unexpected that a tolerable dose of an alpha-adrenergic blocker by the anal route can provide enough relaxation for its application to be clinically useful. Indeed, the response of the internal anal sphincter to adrenergic stimulation is complex in both normal and pathological situations; it is influenced by, and has influences upon, several other neurotransmitters. (Hellstrm et al., Scand J Gastroenterol, 1989 March 24:231-43; Rayner, J Physiol (Lond), 1979 January 286:383-99; Bouvier and Gonella; J Physiol (Lond), 1981 January 310:457-69; Rattan and Thatikunta, Gastroenterology, 1993 September 105:827-36; Carlstedt et al.; Acta Physiol Scand, 1989 January 135:57-64,; Yoshimura et al.; Dig Dis Sci, 1986 November 31:1249-53) Moreover, basal anal canal pressure, at least in some species, does not depend on tonic adrenergic activity and is not altered by administration of an alpha-adrenergic blocker (Culver and Rattan, Am J Physiol, 1986 December 251:G765-71). And, in human subjects studied while under anesthesia for abdominal surgery, stimulation of the hypogastric sympathetic (adrenergic) nerves relaxed the IAS, and administration of an adrenergic blocking drug prevented the relaxation of the sphincter. (Lubowski, et al.; Br J Surg, 1987 August 74:668-70). **Hence, it is by no means obvious that α blockade will reduce IAS pressure sufficiently to relieve pain and promote healing.** [(emphasis added) See Fogel '877, col. 7, lines 12-54.]

Although the Fogel '877 patent was filed (February 25, 1999) after the priority date of the present application, the '877 patent clearly sets forth the factual basis for an absence of any

reasonable expectation with respect to one of ordinary skill in the art at a relevant time period.

In partial summary, both Fogel and Pasricha et al. expressly teach that the complexity of the neural regulation of the IAS and the uncertainties in the mechanisms contributing to IAS muscle associated with anorectal disorders make the art unpredictable. Both show accordingly that one of ordinary skill in the art would **not** have had a reasonable expectation of success that the proposed combination would work.

ii. In addition, Singh et al. directly teach away from the proposed combination with phentolamine:

Although the Action cites Singh et al. as teaching the relaxation of the IAS as the effective way of treating a painful condition associated with the muscle spasm, Applicants have not been able to find the support for such an assertion in Singh et al.

In fact, Singh et al. teach away from the proposed combination. Singh et al. teach the use of vasoconstrictors (see col. 3, line 54 and col. 3 lines 64-67) and list α_1-adrenergic *agonists* (ephedrine, phenylephrine) as suitable *vasoconstrictors* to be used in treating anorectal disorders. **The Action proposes a combination contraindicated by Singh et al.** Phentolamine is a *vasodilator* and an α-adrenergic *antagonist*. Thus, Singh et al. clearly teach away from the use of phentolamine and other α-adrenergic antagonists in treating the subject anorectal disorders.

This teaching of Singh et al. further illustrates the complexity of the subject matter, a complexity which allowed Singh et al. to conclude that an *opposite* activity could be therapeutically useful.

As a whole or individually, the teachings of the Fogel '877 patent, Pasricha et al. and Singh et al. show that a person of ordinary skill in the art would have no reasonable expectation of success with respect to the proposed combination.

iii. Kubota et al. and Bouvier et al. teach very little about the *in vivo* regulation of the IAS tone and taken alone or together do not adequately resolve the above uncertainties so as to provide a reasonable expectation of success:

It is apparent that Kubota et al., did not study the intact internal anal sphincter. They removed the sphincters from the test animals and sliced them into three circular portions and then again these portions were sliced in half (see Methods, p. 174). Kubota then placed the dissected muscles directly in an organ bath. Kubota concluded that sphincter function in the

bath is controlled by both myogenic and neurogenic mechanisms (p. 174, lines 7-15). Kubota et al. studied both the myogenic and neurogenic states. Kubota et al. report: "The pattern of spontaneous electrical and mechanical activity was neither affected by the adrenergic blocking agents (guanethidine 5 x 10^{-6} M) nor tetrodotoxin ...." (see p.177, 1st full paragraph). Thus, the myogenic mechanism appeared to be unaffected by phentolamine.

Kubota et al. also reported phentolamine 10^{-6} M antagonizes the effects of external electrical stimulation on the muscle preparation. Thus, the effect of phentolamine on muscle tone *in vitro* varied according to whether the tone was myogenic or neurogenic. The references cited by the Action do not disclose which of these mechanisms is important to relaxing the IAS in anorectal disorders.

Moreover, with respect to the neurogenic mechanisms, the methodology of Kubota et al. can hardly be described as physiological. The external electrical stimulus activates all of the nerves in the preparation at once. Such stimulation hardly models the more patterned or coordinated neurogenic mechanisms thought to operate *in vivo.*

The results of Bouvier et al. *in vitro* were similar (see Abstract). Bouvier et al. also utilized a quasi-*in vivo* cat preparation to explore the effects of phentolamine on IAS contraction. They surgerized a halothane anesthetized cat to dissect out and ligate the hypogastric nerve. The peripheral end of the nerve was then artificially stimulated with an external electrical pulse (see Methods, p. 458). Bouvier et al. disclosed that in this preparation, phentolamine reduced the response of the IAS to hypogastric nerve stimulation. Bouvier et al. further disclosed that phentolamine neither decreased nor increased the relaxation effect of the parasympathetic nervous system on the IAS. Bouvier et al. also disclosed that phentolamine had no effect on the rectal distention caused inhibition of the anal sphincter muscle activity (see Abstract). Bouvier et al. studied the effects one by one. Where they reported on the non-stimulated or resting state, they found no effect of phentolamine. Bouvier et al. does not teach which of these mechanisms are important to maintaining resting IAS pressure in the intact animal with normal patterns of stimulation. Where they discuss the relative importance of the parasympathetic and sympathetic systems, they state it requires further study (p. 466, last full paragraph).

Moreover, neither Kubota et al. nor Bouvier et al. address the considerations underlying Singh's teaching that α-adrenergic *agonists,* rather than *antagonists,* be used to treat anorectal disorders.

iv. In conclusion, the prior art teachings (Fogel, Pasricha et al. and Singh et al.) relied upon in making the proposed combination with Kubota et al. or Bouvier et al. expressly teach that there is no reasonable expectation of success (Fogel, '877; Pasricha et al.) attached to the proposed combination or, else, present as desirable an effect opposite to that achieved by the proposed combination (Singh et al.).

As the cited prior art does not support a reasonable expectation of success for the proposed combination, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

b. The proposed combination lacks all the elements of the claims

As amended, the base claim recites "a *topical* pharmaceutical composition comprising an α-adrenergic blocker" and "*topically* applying" the composition to the anal region.

Neither Kubota et al. nor Bouvier et al., singly or in combination, teach applying their α-adrenergic antagonists by the topical route to the anal region. Kubota et al. directly exposed their preparation to phentolamine in an organ bath. Bouvier et al. applied phentolamine intravenously. Thus, Bouvier et al. contacted essentially the entire internal milieu of the organism with phentolamine. None of the cited references disclose a *topical* composition of an α-adrenergic blocking agent and none teach or suggest that an α-adrenergic antagonist could be effective as a treatment when topically applied, or even more specifically, could be effective as a treatment of an anorectal disorder when topically applied to the anal region.

As one of ordinary skill would not have a reasonable expectation that the proposed combination would work and as the proposed combination lacks all the elements of the claims, Applicants therefore respectfully request that the above rejections of claims 34-48 under 35 U.S.C. §103(a) be reconsidered and withdrawn.

F. Status of the Petition for an Interference with the Fogel '877 Patent

As amended herein, the pending claims continue to claim the same patentable invention as disclosed in the Fogel '877 patent. The recital of "topical" in the base claim of the present application does not render the subject matter of the pending claims patentably distinct from base claims 1-5 in the Fogel '877 patent. With respect to "topical" for instance, dependent claims 11 and 12 of the Fogel '877 patent recite topical formulations of "a cream, gel, paste, lotion, ointment, ...". Claims 11 and 12 of the Fogel '877 patent multiply depend from each of the base claims in the Fogel '877 patent. Thus, each of the base claims in the Fogel '877 patent read on the "topical" subject matter of the Applicants' claimed invention.

Applicants therefore respectfully request that an interference with the Fogel '877 patent be granted.

G. Summary

Tetrodotoxin and atropine are not α-adrenergic blocking agents. Therefore, the proposed combinations with these agents do not provide all the elements of the claims which recite in part an "α-adrenergic antagonist."

The *prima facie* case with respect to the proposed combination with Kubota et al. or Bouvier et al. with Fogel, Pasricha et al. and Singh et al. is also respectfully traversed. The prior art shows that there was no reasonable expectation of success for the proposed combination (see Fogel '877, Pasricha et al.) and even teaches away from the proposed combination as providing an effect opposite to that taught as being desirable (Singh et al.).

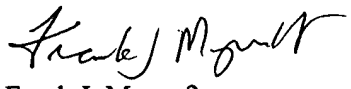
In addition, the proposed combination does not satisfy the recital of a "topical pharmaceutical composition." Neither Kubota et al. or Bouvier et al. taught topical pharmaceutical compositions of an α-adrenergic blocking agent.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants believe all claims now pending in this Application are in proper form for allowance. The Examiner is respectfully requested to issue PTO Form-850 and send the same, along with the application file, to the Board of Patent Appeals and Interferences. Applicants respectfully request that the Examiner declare an interference between the above-referenced patent application and the U.S. Patent No. 6,117,877 and, furthermore, request that the examination of the present application be conducted with special dispatch.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 41 has been canceled without prejudice.

Claims 34, 37 and 42 have been amended as follows:

34. (Amended) A method for treating a patient with a painful condition of the anal region associated with muscle spasm, the method comprising:

providing a topical pharmaceutical composition comprising an α-adrenergic blocker; and

topically applying an effective dose of the composition to the anal region.

37. (Amended) The method of claim 34, wherein said blocker is doxazosin [doxasozin].

42. (Amended) The method of claim 34 [41] wherein said composition [topical preparation] is [a formulation selected from the group consisting of] dry, a liquid, a cream, or an[d] aerosol [formulations].